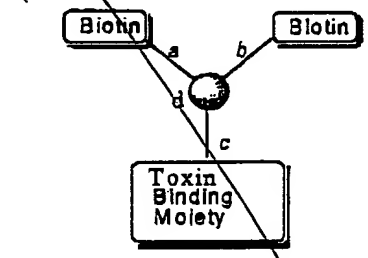
CLAIMS

1. Method for the conditioning of an extracorporeal device for the extraction of toxic material from mammalian body fluids in connection with diagnosis or treatment of a mammalian condition or disease, wherein a solution containing a reagent having the general formula:



wherein the biotin moieties are natural biotin or derivatives thereof,

wherein a, b, and c are linkers, which are same or different, and wherein d is a trifunctional crosslinking moiety,

is passed through a device having biotin binding ability, wherein the reagent is bound to the device, and wherein said device thereby is converted from a biotin binding to a toxic material binding device.

2. Method according to claim 1, wherein the trifunctional cross-linking moiety, containing three functional groups that are nucleophilic or are reactive with nucleophiles, is an aliphatic or aromatic compound, preferably an aromatic compound with 1,3,5-substitution, most preferably derivatives of 1,3,5-benzene tricarboxy-

lic acid, 3,5-diaminobenzoic acid, or 5-amino-1,3-dicarboxybenzene.

3. Method according to claim 1, wherein the toxin binding moiety is a molecule that binds with high affinity to a toxic material with or without an effector molecule and is chosen from the group comprising monoclonal antibodies including fragments or engineered counterparts thereof, aptamers, peptides, oligodeoxynuclosides including binding fragments thereof, intercalation reagents including dyes, chemotherapy agents, natural substances and metal chelates that specifically bind with toxic material with or without an effector molecule or to an effector molecule attached to the toxic material.

4. Method according to claim 1, wherein one or more of the linkers a, b, and c is/are linear or branched and contain(s) water solubilizing functionalities or side groups containing amines, carboxylates or hydroxyl functionalities, preferably an alpha carboxylate or an N-methyl group in a view to improving the stability towards enzymatic cleavage of the biotinamide bond between the biotin moiety or a derivative thereof and the spacer.

5. Method according to claim 1, wherein the biotin derivatives are chosen from the group comprising norbiotin, homobiotin, oxybiotin, iminobiotin, desthiobiotin, diaminobiotin, biotin sulfoxide, biotin sulfone or other biotin molecules having the ability to bind to avidin, streptavidin and derivatives thereof.

6. Method according to claim 4, wherein the linkers a and b provide a minimum of 20 Å and a maximum of 60 Å between the trifunctional cross-linking moiety and each biotin moiety carboxylate carbon atom when measured in a fully linearized form.

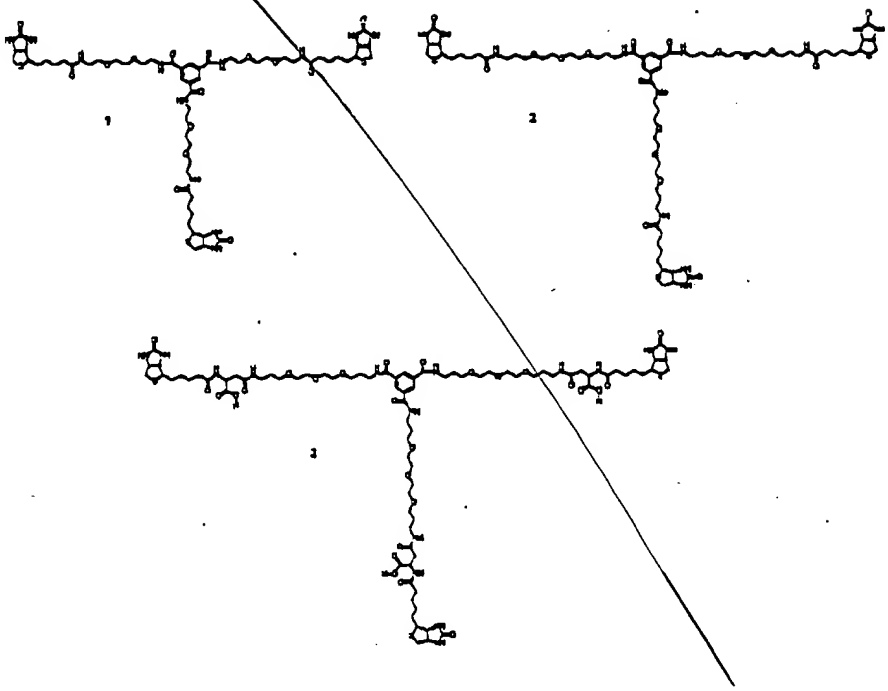
7. Method according to claim 3, wherein the toxin binding moiety has the ability to bind with high affinity to a toxic material chosen from the group comprising metal ions, chemotherapy agents, free radionuclides, radionuclides bound to other compounds, ingested toxins, toxins produced by bacteria, preferably endotoxins or enterotoxins, toxins produced by viral infections, toxins produced by disease states, diseased cells, cells involved in the immune response, anti-blood group antibodies, anti-HLA antibodies, anti-xenoantibodies or any other undesirable endogenous component present in bodily fluid at an undesirable level as a result of a disease, disorder or incompatibility with therapeutic treatment, preferably TNF and cytokinins, or any exogenous component that is or could be involved in a disease, disorder or medical incompatibility, preferably biotin binding molecules.

8. Method according to claim 7, wherein the biotin binding molecule is chosen from the group comprising avidin, streptavidin or derivatives or fragments thereof having essentially the same binding function to biotin as avidin or streptavidin, and is optionally bound to an effector molecule.

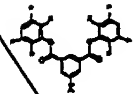
9. Mehtod according to claim 3, wherein the effector molecule is a radionuclide, a cytotoxic agent, a chelating agent for binding of radionuclides, a chemotherapy agent, a natural toxin or a derivative thereof, or a synthetic toxin.

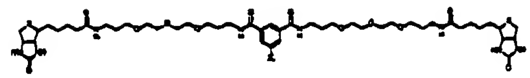
10. Method according to any of the previous claims, wherein the toxin binding moiety is biotin, the spacers a, b, and c are 4, 7, 10-trioxa-1,13-tridecanediamine and the trifunctional cross-linking moiety is 5-amino-1,3-dicarboxybenzene.

11. Method according to any of the claims 1-9, wherein it is

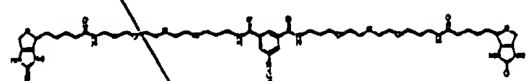


Sub A' cont.

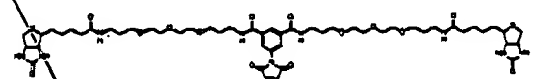




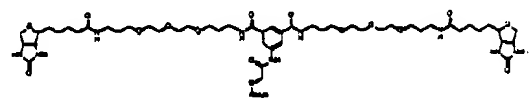
5: X = NH-tBoc
6: X = NH2



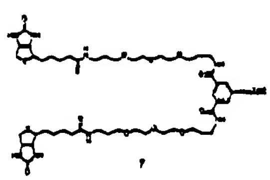
7



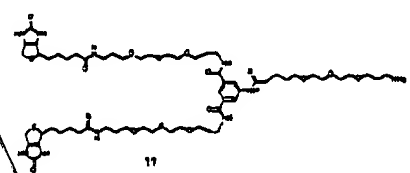
8



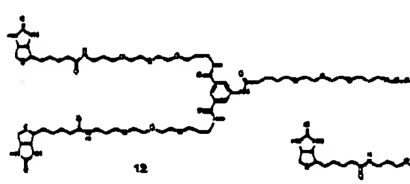
9: X = tBoc
10: X = H



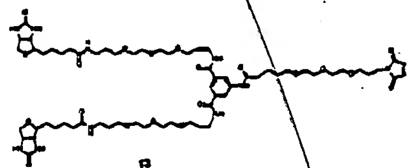
7



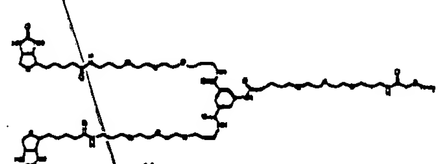
11



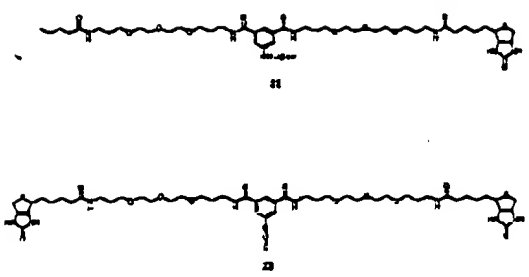
12



13



14



12. Method for the extracorporeal extraction of toxic material from mammalian body fluids in connection with diagnosis or treatment of a mammalian condition or disease, wherein the toxic material, optionally including an effector molecule, which has been added to the blood circulation of a mammal and kept therein for a certain time in order to be concentrated to target tissue or cells but which have not been concentrated to said target tissue or cells, directly or through other previously administered molecules, is completely or partially cleared from the blood circulation by passing the mammalian blood or plasma through an extracorporeal device containing a reagent as defined in any one of claims 1-11.

13. Method according to claim 12, wherein the toxin binding moiety of the reagent is biotin or a derivative thereof, wherein

a) biotinylated targeting biomolecules added to the blood circulation of the mammal but not concentrated to the target tissue or cells are cleared from the blood circulation by passage through an extracorporeal biotin-binding device, and

b) biotin-binding molecules, administered to the blood circulation after step a), each conjugated to an effector molecule, but not concentrated to the target tissue or cells, are cleared from the blood circulation

by passage through an extracorporeal device containing said reagent for specific adsorption of the biotin-bindning molecules and the effector molecules conjugated thereto.

14. Method according to claim 13, wherein

a) the biotinylated targeting biomolecules each are conjugated with an effector molecule, and which have been administered to the blood circulation in order to monitor the tumor uptake by detection of the effector molecule by a gamma-camera, PET-scan, MRI or other in vivo diagnostic techniques, and wherein the effector molecule in step b) is a cell killing radionuclide or a cytotoxic agent.

15. Method according to claim 13, wherein in step b) the biotin-binding molecules are not conjugated to effector molecules, and in a further step c) a conjugate between an effector molecule and biotin or the reagent is added to the blood circulation of the mammal, and, optionally, the blood is cleared from said conjugate not concentrated to the target or tissue cells by passage through an extracorporeal biotin-binding device.

16. Method according to claim 12, wherein the toxin binding moiety of the reagent is biotin or a derivative thereof, wherein

a) biotin-binding molecules attached to targeting molecules added to the blood circulation of the mammal but not concentrated to the target tissue or cells are cleared from the blood circulation by passage through an extracorporeal device containing said reagent for specific adsorption of the biotin-binding molecules, and, optionally,

b) biotinylated molecules, either with biotin or with the reagent, administered to the blood circulation after step a), each conjugated to an effector molecule,

but not concentrated to the target tissue or cells, are cleared from the blood circulation by passage through an extracorporeal biotin-binding device.

17. Method according to any of claims 13-16, wherein the biotinylated targeting biomolecules are targeting molecules containing natural biotin or derivatives thereof,

the biotin-binding molecules are molecules containing avidin, streptavidin or derivatives thereof,

the biotinylated molecules are radiolabelled biotin derivatives containing a radiometal chelation moiety, and

the effector molecule is a radionuclide or a cytotoxic agent.

18. Method according to claim 12 for the simultaneous blood clearance of multiple anti-HLA antibodies, multiple anti-blood group antibodies or multiple anti-xenoantibodies, preferably prior to organ or cell transplantation, wherein it comprises an extracorporeal device containing said reagent or several reagents having different specific toxin binding moieties.

19. Extracorporeal device for the extraction of toxic material from mammalian body fluids in connection with diagnosis or treatment of a mammalian condition or disease, wherein it comprises a biotin binding molecule bound to a reagent as specified in any one of claims 1-11.

20. Extracorporeal device according to claim 19, wherein the device is a column, the biotin binding molecule is avidin or streptavidin and the reagent is a tribiotinylated reagent.

add A2